FOSTERING COMMUNICATION AND COLLABORATION

The NIH CATALYST

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NIH Sees Silver Lining In COPR

by Celia Hooper and Fran Pollner

From the outset, NIH Director Harold Varmus gently hinted that creating a new advisory group of public representatives was not exactly his idea. But in opening comments at the first meeting of the Committee of Public Representatives (COPR, or "Copper") on April 21, Varmus indicated he now embraces the new committee and plans to test its mettle.

The idea for COPR had its origins in an Institute of Medicine (IOM) report that capped a congressionally mandated study of how NIH sets its research priorities and interacts with the public. Two or three years ago, Varmus said, Congress was contemplating major increases in NIH's budget but wanted to be sure that this largess was well-spent from all points of view. Doubting that word about the treasures of NIH research was indeed reaching the ears of their constituents, Congress directed the IOM to conduct the study.

COPR participants bid NIH director Harold Varmus adieu at meeting's end.

For its part, the IOM produced a report in which lay the seeds of COPR, Varmus said. Despite the presence of public members on advisory panels to the NIH director and to the institutes and centers—and despite the steady presence of disease interest groups at the NIH campus—the IOM deemed NIH's interaction with the public insufficient.

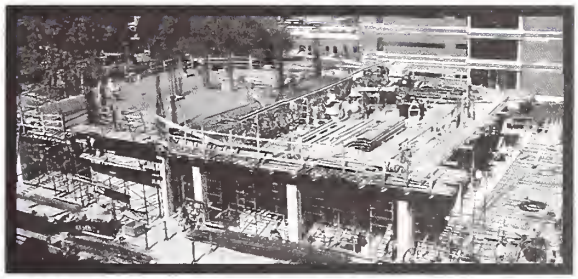
An ad hoc group appointed from

continued on page 4

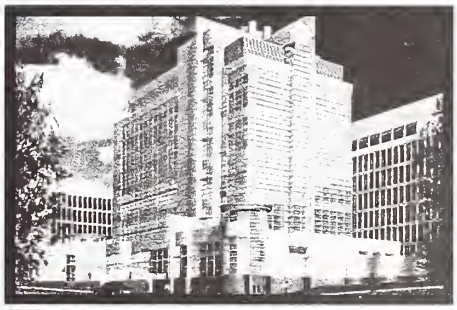
Vaccine Research Center Rising As New Director Takes Stock

by Doug Loftus

Since construction of the new Vaccine Research Center (VRC) began last year, people working in Buildings 36 and 37 have been front row spectators to a large-scale creative endeavor. Amid noise and a seemingly chaotic array of equipment, cables, concrete, and steel, specialized teams of craftsmen methodically coordinate their activities, progressively building from the foundation upward. When finished, the product of their efforts will benefit not only the research community, but, it is hoped, public health as well. The creation of the VRC itself serves as a fitting metaphor for the planned activities of its future occupants, according to the vision set forth by VRC Director Gary Nabel at the Office of AIDS Research Advisory Council (OARAC) meeting held April 28–29.



Fran Pollner



The Vaccine Research Center: *In the throes of development in the spring of 1999 (above) and as it is projected to appear in splendid completion in the summer of 2000 (below).*

Nabel, who has been a Hughes Investigator at the University of Michigan, Ann Arbor, as well as director of the Center for Gene Therapy there, has a strong and diverse background in research and medicine, though vaccine development has not been the focus of his career. "I do actually think there is an advantage to the fact that I wasn't in traditional vaccine development—I understand the issues, but I think I can come in with more of an open mind and try to facilitate things based on my background," he says.

The background he speaks of includes innovative work on molecular biological strategies and their application to gene-based therapies and vaccinations for AIDS, cancer, and Ebola virus.

He was drawn to the VRC position by the "enormity and challenge of the problem—the unrelenting spread of AIDS and the daunting task of developing a vaccine"—a mission that blended the bench and bedside aspirations of his scientific pursuits. He also realized that rather than remaining

continued on page 5

CONTENTS

Vaccine Development at NIH: VRC Rises on the Shoulders of Giants

Richard G. Wyatt

When, in a 1997 commencement address, the President called for creation of the Vaccine Research Center at NIH, he chose to place it in an institution with a rich history in vaccine development. Because NIH has its roots in the Public Health Service, development of vaccines and prevention of disease have been appropriately a part of our history nearly since NIH was founded in 1887.

In 1895, Joseph Kinyoun, the first head of the Hygienic Laboratory, NIH's precursor organization, worked on diphtheria antitoxin that had just been developed in Europe. The Laboratory was later charged in 1902 with responsibility to test the purity of vaccines and antitoxins, because of concerns about contamination of biologicals.

These efforts remained a part of NIH until 1972, when they were transferred to the Food and Drug Administration. They remain an integral part of vaccine efforts today as a part of the FDA's Center for Biologics Evaluation and Research on the NIH campus. These early activities of the PHS and its Hygienic Laboratory stimulated some of the first work in basic immunology because of anaphylactic reactions to biological products.

Later, intramural investigators, working at the NIH Rocky Mountain Laboratory (RML) in Montana, succeeded in preparing a chemically inactivated vaccine against Rocky Mountain spotted fever (RMSF) in 1925. This crude vaccine was made of ground-up, infected ticks and was used widely in Western states. Improvements followed when Herald Cox grew rickettsia at RML in eggs; this led to an improved RMSF vaccine and also to a typhus vaccine that was needed during WWII. Troops were also immunized during WWII with an improved yellow fever vaccine developed at RML in 1943 by Mason Hargett; the new versions avoided earlier problems associated with producing yellow fever vaccine with human serum. Further, the standardization of the initial cellular pertussis vaccine and of allergens was first achieved at the NIH Division of Biologics in the 1940s.

But we need not look only at the past to find legendary intramural investigators who have committed their scientific careers to the pursuit of vaccines. Now as then, persistence is a hallmark of NIH efforts that could well be compiled as a modern sequel to *Microbe Hunters,* Paul de Kruif's 1926 classic that has, over the years, inspired more than a few students to develop vaccines for future generations.

Vaccine research is undeniably a high-risk endeavor—not a field for the faint of heart. But it is also an endeavor whose success is measured in enormous benefit to the public health. There are many examples of highly successful vaccines that have been developed in NIH intramural programs and deployed into the world: a live, attenuated adenovirus vaccine to combat respiratory disease in military recruits (1962), developed by Robert Chanock and Robert Huebner; *Haemophilus influenzae* type b vaccine (1988) and Vi vaccine for typhoid fever (1991), developed by Margaret Pittman, John Robbins, and Rachel Schneerson; an acellular pertussis toxoid (1998), prepared by Robbins and Ronald Sekura; hepatitis A vaccine (1985), developed by Robert Purcell and co-workers; and a tetravalent rotavirus vaccine (1998) development effort, led by Albert Kapikian.

Beyond these vaccines that have been brought to fruition are many others still moving through the pipeline: vaccines against respiratory syncytial virus, influenza virus, parainfluenza virus, hepatitis E virus, pneumococcus, group B streptococcus, meningococcus, shigella, and *Escherichia coli* O157, as well as a series of cancer vaccines under development in NCI, such as a papillomavirus vaccine.

> **Vaccine research is . . . not a field for the faint of heart. But it is also [one] whose success is measured in enormous benefit to the public health. There are many examples of highly successful vaccines developed in NIH intramural programs and deployed into the world. . . .**

During just the past decade, there have been approximately 200 invention reports submitted to NIH tech transfer offices on proposed vaccines developed by NIH intramural scientists. Several have already led to patents, and an astonishing 10 licenses have already been issued to companies that anticipate turning these NIH discoveries into commercial vaccines.

It is out of this rich legacy and churning activity that we now launch the Vaccine Research Center [see article, page 1]. With the VRC's infusion of direction and synergy, the future holds the exciting prospect of new focus and discovery that will lead to safe and effective vaccines against HIV/AIDS. We can be optimistic, based on historical precedent, that the desired HIV/AIDS vaccines will indeed emerge if investigators persist and remain committed to the field.

The tradition and commitment of secure, long-term funding and support from NIH leadership, in turn, will help to undergird our researchers' determination as we strive to maintain the creative, stable, and inspirational milieu from which the work to create safe and effective vaccines against HIV/AIDS—and tuberculosis, malaria, and other major pathogens—can be pursued to success ■

—Richard G. Wyatt
Executive Director, OIR

Catalytic Reactions

On an NIH Academy

Michael: I read with interest the recent (March-April 1999) *Catalyst* containing the article by Joan [Schwartz] on mentoring and your very thoughtful commentary on the proposed NIH Academy. After thinking a lot about both, I'd like to share some comments with you.

You, and others of us, have emphasized the critical role that mentoring plays in the success of young investigators, and the *Guide* [*Guide to Training and Mentoring in the Intramural Research Program*] certainly will be an important asset. In your commentary, you mention the Slavkin report and the need for more scientists from disadvantaged backgrounds "to help guarantee more attention to research problems related to health disparities." Many have spoken and written of the need for more minority scientists as participants in all phases of the fight against minority health disparities, including roles as health care providers, policy makers, administrators, researchers, and educators. In my opinion, this is not a problem that NIH can, or would be expected to, take a lead in solving. Rather, academic institutions across the country need to expand their training of minority scientists in a variety of health disciplines.

You also mentioned the problem we at NIH have in recruiting proportionate numbers of minority scientists for "junior and senior faculty" positions. This is, indeed, our problem, and you cite the Slavkin report's recommendation of how the proposed Academy *would* address it. You make a very cogent argument for the Academy, and I agree with it.

You mention all the important activities that might be undertaken by the Academy. However, what is missing, and in my opinion glaringly so, is any reference to another issue that you and I have discussed—how to improve the atmosphere for and success of those minority scientists who come here. How will one influence the performance of senior DIR scientists, specifically the lab chiefs, so that young minority scientists do not face additional impediments to succeeding in the competition for tenure-track spots? What exactly are you proposing to do with the principal investigators other than distributing to them the mentoring *Guide*?

I am confident that you will not feel that my comments in any way detract from my opinion of the excellent work you are doing towards achieving the goal of increasing the number of minority scientists in the upper levels of the NIH intramural program.

I am not Lewis Thomas, nor am I listening to Mahler at the moment, but these are my late-night musings, for what they are worth.

—George Counts, NIAID

Dear George,

I am most grateful for your comments and ideas concerning the NIH Academy concept. One comment, in particular, strikes me as the key to success—changing the attitude of some of our supervisors toward their trainees. The goal of the NIH Academy will be to provide whatever support is needed at NIH to optimize the possibility of success.

As you know, I am establishing a working group of intramural scientists, NIH educators, and administrators who, like yourself, have been dedicated to improving mentoring and training at the NIH. Arlyn Garcia-Perez and Levon Parker have agreed to chair this group. I look forward to our working together on this very exciting and challenging pathway to our NIH Academy.

—Michael Gottesman, DDIR

On an NIH Graduate School

I am responding to two of the items in the "Catalytic Reactions" section of the March-April *NIH Catalyst*.

First, I would like to see a small NIH graduate school, but only if the NIH infrastructure is adjusted to support such a program. I would suggest that the program be a partnership between one or more universities (for example, Johns Hopkins University), so that essential courses would be taken at that university and tutorial training and research would be conducted at the NIH proper. NIH faculty who participated in this program would be on the university faculty as adjunct or regular members. A number of infrastructural changes would be required to accommodate the introduction of a graduate school. I would suggest that the NIH create extra slots to accommodate these students so that they don't compete with existing FTEs. Of course, an administrative support staff would have to be created to manage the graduate program. An NIH curriculum focusing on cross-discipline areas of research (that is, driven by a particular research question or clinical entity) would be developed. Where will the courses be taught? Additional space and funding for furniture and computers to accommodate the graduate students would have to be identified and justified.

I would be interested in serving on such a faculty and would be willing to serve on a committee planning the graduate program.

Second, mentoring is a skill, and it's an important part of the training of junior faculty, fellows, and students. It is also a responsibility that each investigator should take seriously. Mentoring is not a perfect art, and it is possible to improve your mentoring ability as you gain more experience in supervising trainees. Being mentored is one of the most memorable experiences a trainee can have; relationships formed as a result of this experience can be very rewarding and last a lifetime. NIH should offer the possibility of programmatic training in mentoring for interested staff.

—Jordan Grafman, NINDS

We are beginning the process of defining a graduate program for NIH that takes advantage of the enormous research talent here, especially in translational research and bioinformatics, and allows us the flexibility to create a new curriculum in areas currently not generally taught in existing graduate programs. The details of the program are not determined, and we will be seeking the expertise and counsel of the entire NIH community and the greater academic community as we design a novel graduate program at NIH. Improved mentoring will be an important goal of this program.

—Michael Gottesman, DDIR

Some Anonymous Tips

Major objectives of an NIH Academy: Train postdocs in clinical research. No undergraduate or high school training should be provided.

Is there a need for a graduate school: Since we have USUHS across the street, which already is accredited and has infrastructure and staff in place, that should be utilized. A limited PhD program already exists, and they have the room to expand.

Is the emphasis on mentoring appropriate, and should mentoring skills be taught: Yes, it is important. However, the PIs at NIH will not attend training.

Suggestions for improving *The NIH Catalyst*: Print people's feedback.

—Anonymous

Sure. So long as we get the last word—Ed.

The COPR Silver Lining

continued from page 1

a list of people familiar with NIH met with Varmus in September. The group recommended that the citizens' committee that would be named COPR include a broad mix of members—patients, scientists, administrators, advocates—and that the NIH director have the last word on selection.

To counteract what seemed at first like a prescription for factionalism, Varmus set stringent selection criteria, including the ability to think globally, exercise leadership, analyze problems, communicate well, and work effectively in a group. An ad was posted in the *Federal Register* and e-mails went out to all of the institutes' contacts in every constituency group. Other federal agencies helped spread the word, and special attention was paid to recruiting members representative of minority groups. "The word got out there," says NIH Communications Director, Anne Thomas, charged with coordinating COPR's activities. The ads and letters drew 250 applications, many of them glittering.

In fact, Varmus was so impressed with the quality of the applications that picking the final group of 20 was very difficult. Unwilling to cut the remaining applicants loose, Varmus invited all 230 to become "COPR Associates." He told the COPR members that he envisions the "Associates" as a place to which COPR members might "retire" and from which new members might be drawn. He said he expects to let the Associates group largely run itself, serving as a conduit to and from the general public, much like the official group. Thomas says she has already had requests from institutes for help and advice from COPR associates.

The credentials of the COPR proper shine like a new penny. The members went around the table, introducing themselves to one another (see below) and the assorted onlookers that made up the audience to this open meeting. Some had prior experience serving on NIH advisory groups; some had been involved in NIH-funded research—either as principal investigators or clinical trial participants; some were afflicted with the disease that dominated their advocacy work; none was a stranger to the complexity of competing and overlapping interests in health research policy and funding; and some made a point of affirming their willingness to cast a wider net of concern than their particular bailiwick during their COPR service.

The COPR Plate

Debra Lappin (Colorado), a lawyer and longtime Arthritis Foundation officer, policymaker, and advocate instrumental in crafting the National Arthritis Action Plan, expressed her desire that COPR have "input into the research priority-setting process."

Isaac Montoya (Texas), think tank president, university professor, and behavioral scientist with a focus on health services research to improve the health status of underserved populations, cited "migrant workers and drug abusers" among his special concerns.

Rosemary Quigley (Michigan), whose work in research ethics has served an NIH-funded project on genome technology and reproduction, as well as the AMA and her home state, described herself as the "20-something on the panel" whose experience as a cystic fibrosis patient and research volunteer would inform her efforts to "balance the cult of the cure with an understanding of what it means to have a chronic genetic illness."

Theodore Castele (Ohio), self-described "70-something on the panel," is a radiologist and health reporter ("Dr. Ted") for a Cleveland television station who said he looked forward to being able to tell the public about the "great things going on at NIH."

Robin Chin (Rhode Island), a pharmacist, HIV/AIDS advocate, and member of the National Asian Women's Health Organization with personal and family experiences of breast cancer and diabetes, said one of her primary goals is to "eliminate health disparities among minorities."

Barbara Lackritz (Missouri), a speech pathologist whose Internet activities maintaining cancer support lists put her in touch with more than 30,000 patients and care givers, noted that her own illness and those of family members contribute to the "broad-based perspective" she brings to COPR.

Michael Anderson (Oklahoma), a minister and cofounder of the Presbyterian Health Foundation whose chief interests are medical education and research and biotechnology transfer, spoke of his own desire to "apply science to human enterprise" and noted that the Human Genome Project represents a "significant ethical opportunity."

Melanie Dreher (Iowa), a nursing school dean and anthropologist, counted rural health, especially among the elderly and isolated, chronic illness, and the effect of global migration on health among her professional interests and observed that as a member of an NIH study section and a clinical trial participant, she understands "how important NIH is to the public and how NIH's strength derives from the public."

Luz Claudio (New York), who described herself as the "basic science nerd of the group," is a neuroscientist at the Mount Sinai School of Medicine whose research includes environmental effects on the brain and whose community outreach activities are focused on training programs for disadvantaged and minority youth.

Douglas Yee (Hawaii), a financial advisor and the founder of the research committee of the American Lung Association of Hawaii, whose business acumen has been applied to reducing health disparities in his state, expressed his enthusiasm for working cooperatively with fellow panelists.

Vicki Kalabokes (California), cochair of the Coalition of Patient Advocates for Skin Disease Research, helped promote the creation of the six NIAMS skin disease core centers but said that her interests lie in nearly every disease and in promoting the "good of the whole."

Roland McFarland (California), a television programming analyst and representative of the Los Angeles and Hollywood Entertainment Council, told the group that the directors', screenwriters', actors', and producers' guilds had just formed a council on public health issues and "will work with NIH to get the word out."

Thomas Vaalburg (Michigan), a former health care executive involved in the development and marketing of medical devices, pointed to cancer and bipolar disorder as two areas of special interest to him and pinpointed his goal as "to serve the underserved."

Joan Lancaster (Tennessee), director of government relations at the Johnson City Medical Center and involved in the planning and development of a Regional Med-Tech Center, placed her primary concern in access to health care for rural America, especially among the elderly.

Pam Fernandes (Massachusetts), a member of the first team of blind marathon runners in the United States who ran in the Boston Marathon a week before the COPR meeting, credited biomedical research with her "being here today" and emphasized the need for public education about such matters as the role of exercise in controlling diabetes.

Robert Roehr (Washington, D.C.), a medical reporter who has written extensively on HIV/AIDS, tuberculosis, vaccine development, genetics, and other medical topics, as well as meetings at NIH and other agencies, presented his goal as "making NIH research available at the patient level."

Lydia Lewis (Illinois), executive director of the National Depressive and Manic-Depressive Association, with 20 million constituents, and a member of the NIH task force overseeing a clinical trial of St. John's wort, said she wanted NIH to focus its priorities "where there is the most promise of therapy and cure," as well as to be more sensitive to the way illness can be stigmatizing.

Maurice Rabb (Illinois), an ophthalmologist and clinical investigator who served on the NEI Advisory Council and NIH Sickle Cell Disease Advisory Council, emphasized the need to recruit and retain minority faculty and assigned himself the task of catalyzing interactions among NIH, medical organizations, and outreach communities.

David Frohnmayer (Oregon), president of the University of Oregon who spoke via conference call, extolled NIH as an "international treasure" and told the group of the loss of family members to Fanconi's anemia and his desire to "understand molecular medicine and gene therapy."

Mary desVignes-Kendrick (Texas), a pediatrician and director of Houston's Health and Human Services department, who was unable to attend the first meeting, has cited narrowing the outcome disparities between ethnic groups as a major objective. ■

VRC To Be

Varmus told the group that serving on the committee would be no free ride. In addition to meetings twice a year, he expects COPR to have a constant dialogue with NIH, either through him or through Thomas. He expects COPR members to serve on advisory and review panels, conduct studies and analyses, lead the COPR associates, and evaluate how well NIH manages its relations with the public and constituency groups.

Just as he has put his Advisory Committee to the Director to work on technical and scientific issues, Varmus said, COPR members can expect to roll up their shirtsleeves on issues that pertain to the public, to patient populations, and public health. Examples include ethical issues, privacy of medical information, and embryo research, Varmus said.

Underscoring his intention to mine the COPR, Varmus asked the group to stipulate those activities they would want to involve themselves in "in a more intense way" and noted that the next COPR meeting would likely include a report back to the group of discussions arising during a "budget retreat" slated for June, as well as address the protection of research subjects, complementary and alternative medicine, and how to expand access to the "remarkable resources of the Internet and make the whole nation interactive." Additional items suggested by COPR members included technology transfer, the Human Genome Project, and the logistics and ethics of research conducted abroad—especially vaccine research. ■

VRC Rising

continued from page 1

strictly focused on gene therapy, but "using many of the same approaches, applying much of the background I've acquired toward HIV vaccine development, I could potentially make a much greater impact." The NIH leadership and the intellectual and material resources available in the strong intramural programs of basic immunology, virology, and structural biology proved a powerful lure as well, he says.

The VRC mission—ultimately the creation of a candidate HIV vaccine (or vaccines)—actually is twofold, according to Nabel. He believes that the advancement of basic science in virology and immunology will necessarily generate clinical gains. As he puts it, "It's an opportunity to do good science and do some good. It's not one or the other—it's both." As he broadly outlined the planned endeavors of the VRC to OARAC members, it became apparent that the Center will occupy a rather unique niche on the NIH campus.

The VRC's functions will include both research *and* development directed toward a very specific goal, prompting one Advisory Council member to ask whether NIH will be hosting a medical "Manhattan project" of sorts. Although Nabel doesn't view it that way, he acknowledges that the VRC will be organized in a manner unlike most institutes and laboratories on campus (athough such efforts are not without precedent at NIH; see "Vaccine Pursuit Accelerated in NIAID Malaria Research Program," *The NIH Catalyst*, March-April 1999, page 8).

Nabel anticipates about 100 full-time slots, with perhaps 15 senior and junior investigators, and an additional 50 postdocs. Personnel will function in three major areas: basic research, a core analytical and production (including GLP) facility, and clinical and regulatory affairs. He expects that VRC operations in these areas will greatly benefit from strong partnerships with intramural and extramural scientists, with private biotech and pharmaceutical companies, and with the FDA as well. The challenge of creating an effective HIV vaccine, Nabel believes, demands idea sharing across the public and private sectors.

Once the Center is staffed, the goal is to apply all available resources to bring candidates to Phase I trials on campus. At the immunological level, this means producing vaccines with the capacity to elicit effective antibody and cytotoxic T lymphocyte responses. Nabel anticipates that much information can be gained testing formulations among HIV seropositive individuals but that, ultimately, a truly protective vaccine—vs. one designed for therapy—is a more realistic goal.

On the subject of realism, Nabel is asked how he views President Clinton's challenge to develop an HIV vaccine within 10 years. He says he sees it as a "useful benchmark," a reasonable period of time in which to determine "whether it can be done or not and to figure out where to go from there." ■

Ready for E-biomed?

A modest proposal put forth by NIH Director Harold Varmus and others would transport the geographically and thematically separated realms of scientific publications into the singular universe of cyberspace, where both strict peer review and a more casual process would speed papers to the eyes of the world at large. Check out the proposal at

<http://www.nih.gov/welcome/director/ebiomed/ebiomed.htm>.

Some journals have printed news stories about E-biomed, including *Nature* (**398:** 725, April 29, 1999) and *Science* (**284:** 718, April 30, 1999). ■

Poster Call for Fall Festival

The time has come for all NIH and FDA staff based at the Bethesda campus to submit poster abstracts for the 1999 NIH Research Festival.

Poster applications must be submitted online; the form can be accessed at the Festival web site at

<http://www.nhgri.nih.gov/festival99/poster_registration.html>.

The deadline for submission of poster topics is 5:00 p.m., Friday, **June 18**. Abstract receipt will be acknowledged by e-mail, and applicants will be notified of acceptance by mid-July.

The NIH Research Festival is the annual showcase for the NIH intramural program. A Postdoctoral Job Fair, sponsored by the Office of Education, will kick off the Festival on Tuesday, October 5, with plenary sessions and mini-symposia following on October 6 and 7. Poster session themes generally correspond to those of each day's plenary session and mini-symposia. This year's plenaries focus on advances in transplantation research, gene therapy, and medical imaging.

For further information about poster registration, contact Paula Cohen at 6-1776 or e-mail **<pc68v@nih.gov>**. ■

VRC Director Gary Nabel's Correlates of Collegiality

by Fran Pollner

Connections and collaborations are the heart of the Vaccine Research Center (VRC), as its new director, Gary Nabel sees it and, he says, as its objectives demand. Though he is still based at the University of Michigan in Ann Arbor, where he is director of the Center for Gene Therapy and a Howard Hughes Medical Institute investigator, Nabel's official start date as VRC director was April 11—and he's been commuting to Bethesda, a situation that will persist until the VRC is ready for occupancy around August 2000. At that time, he will move his lab and "a dozen or so" of his colleagues—as well as some Ebola virus vaccine candidates his lab has been working on—to the VRC.

On campus, when the VRC rises whole from its scaffoldings, it will take its place as Building 40, adjacent to Building 37. In Nabel's schematic view, the VRC would be an inner circle with connecting threads to surrounding circles representing the AIDS research enterprises at the NCI Frederick Cancer Research and Development Center; the intramural research programs throughout NIH that touch upon AIDS, vaccinology, immunology, virology, and other related investigations; the biotechnology and pharmaceutical industries; and, with perhaps less compelling tugs, other federal agencies and academia.

Within the first weeks of his "arrival" here, Nabel navigated a weekend VRC strategic planning retreat and attended the semiannual meeting of the Office of AIDS Research Advisory Council (OARAC) meeting. In his presentation and discussions with OARAC members and a subsequent interview with *The NIH Catalyst*, Nabel addressed an array of issues related to VRC infrastructure, its relation to the rest of NIH and the vaccine marketplace, and the characteristics of an acceptable AIDS vaccine.

Inside the VRC

Though these are the "early days of assembling the VRC organization," Nabel has a pretty clear idea of the composition of the Center. Intramural investigators at NIH whose research has bearing on AIDS vaccine research will almost certainly remain in their current labs, linking into the VRC by using its core facilities, having a postdoc presence there, and attending seminars. "Our expectation is that a minority of NIH investigators will choose to come over—I actually have not met anyone yet from the intramural program who wants to. But any who do would go through the same selection process as extramural researchers who respond to our ads." Nabel estimates that 80 percent of VRC scientists will be recruited from outside NIH. "I know it's not a trivial thing to move, but I've had inquiries from people who have reason to be content where they are," he comments. Anyone recruited before the VRC is ready for occupancy can begin their research "in situ" and be placed on the NIH payroll immediately. Nabel expects that when the building does open, it will be filled with many investigators whose VRC research is already in progress.

Gary Nabel

Of the 100 full-time positions available, perhaps 15 will be administrative personnel; the remainder, he said, will be researchers, probably two-thirds of whom will be involved in preclinical (virology, immunology, translational) research and one-third in clinical trials analysis and development. Much of the production work will be conducted on contract, and clinical trial activities will take place at the Clinical Research Center.

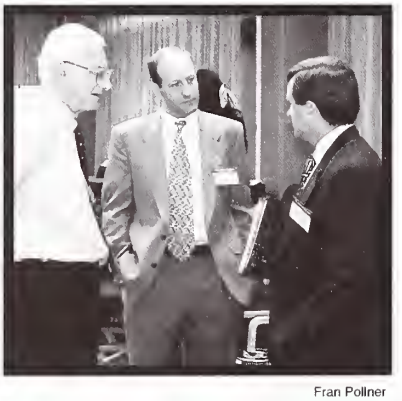
As for the breakdown in numbers among the preclinical researchers, "it will probably be an even three-way split between virology, immunology, and translational research," he said—and they will all be "outstanding scientists, collegial, and able to look at things critically." One other desirable quality, he added, is that they "have a passion to develop an effective AIDS vaccine. Without passion and drive, it will be difficult to move beyond the many obstacles that will face us."

The VRC budget, which is $16 million this year, will have risen to about $30 million a year by the time the building is fully occupied and working at capacity, Nabel said.

Outside the VRC

The efforts of the VRC and existing NIH vaccine research will complement one another, Nabel said, noting that by no means would all vaccine work be going on in one building and citing as examples vaccine research in malaria in Lou Miller's NIAID lab, bacteria in John Robbins' NICHD lab, and viruses in Robert Chanock's NIAID lab.

He also pointed to the "excellent potential for synergies" with two groups at the NCI's Frederick Cancer Research and Development Center: John Coffin's viral resistance program, which is exploring the molecular basis for resistance mutations and viral heterogeneity, and Larry Arthur's AIDS vaccine program, which has "been at the forefront of whole-virus production efforts" and is exploring ways to chemically inactive whole virus and use it as an immunogen.



Fran Pollner

Betwixt and Between: *As the OARAC meeting adjourns at the end of its first day, Gary Nabel (center) continues discussions with Neal Nathanson (left), OAR director, and James Curran (right), director of the Emory-Atlanta Center for AIDS Research and head of the OARAC prevention science working group. During the meeting, Nathanson noted that the 1999 budget included a 30 percent increase in AIDS vaccine research and listed among his own research priorities "more products in Phase I trials, more primate models, methods to measure cellular immunity and induce neutralizing antibodies, and more work on replicons and vectors." Curran had observed, with pleasure, that "NIH is finally coming together (with a) goal-driven scientific agenda for vaccine research."*

Nabel sees a VRC role in developing core technologies of value to all vaccine research and working with vaccine-involved NIH researchers to implement them. "We want to take advantage of opportunities that present themselves but not be distracted from our central mission, which is to advance AIDS vaccine candidates," he said.

On the other hand, the VRC will not have to create certain resources that already

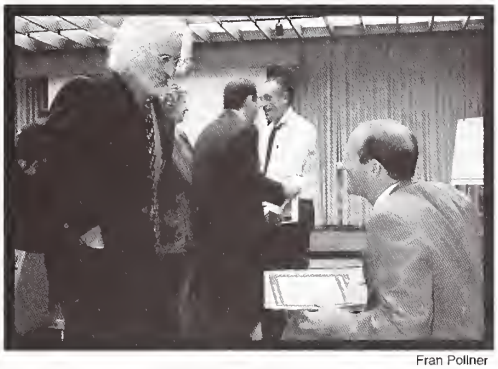
exist on campus and that VRC researchers will be able to tap into—such as the structural biology apparatus of the Intramural AIDS-Targeted Antiviral Program, the NIAMS Protein Expression lab, and the services of the ORS Bioengineering and Physical Science Program.

On the issue of vaccine production itself, Nabel noted that NCI's full-scale manufacturing facility at its Frederick site, which provides products for NCI clinical trials, could be a model for the VRC—should the VRC decide to develop a parallel capacity for HIV vaccine candidates. "That's a question that we'll probably explore further. Basically, we're trying to create a diversified set of mechanisms, from a low-tech model that gives us the ability to manufacture on site to contracting out to creating an expanded production facility here. We don't want to exclude any possibility." Somewhat reluctant to entrust product manufacturing to offsite entities, he said he will nonetheless pursue outside contracting aggressively, with appropriate oversight mechanisms. He anticipates extensive collaboration with the biotechnology and pharmaceutical industries to improve clinical assays and production techniques, and he plans to hold regular NIH-industry meetings and to organize a "pharm/biotech consortium" and even to "steal some people from industry on the translational side."

Fran Pollner

Good Vibes: *OAR director Neal Nathanson (left) and VRC director Gary Nabel*

As for on-site animal research, the VRC has "space for more mice than people by a factor of 80," Nabel said. And although there's no on-site primate capability, the VRC has access to NIH's Poolesville resources. Beyond the VRC's milieu of preclinical work, vaccine concept, and human immunology, once a candidate vaccine is ready for human testing, the FDA will help with Phase I pharmacology and toxicology guidelines, and the VRC will "hand it off" to NIAID's newly established AIDS Vaccine Trial Network. Asked from which base the PI would come—the VRC or the VTN—Nabel replied, "I would love to have that problem to deal with. It doesn't really matter."



Fran Pollner

More To Come: *OARAC member Philip Greenberg (left), professor of medicine at the University of Washington School of Medicine in Seattle, continues dialogue with Gary Nabel (seated) at day's end. Greenberg had characterized the VRC as "halfway between a biotech company and an academic initiative." At rear is OARAC member William Snow, of the AIDS Vaccine Advocacy Coalition, who expressed elation over the "revitalization" of an HIV vaccine as a research priority. "We've gone from last to first," he commented on the agenda order of delivery of working group reports.*

Inside the Vaccine

Another problem raised during the OARAC meeting pitted the relative value of a vaccine that offered complete protection for part of a given vaccinated population vs. one that afforded partial protection for all those vaccinated. Using gay men in San Francisco as a model vaccinated population, Sally Blower, an associate professor of microbiology and immunology at the University of California at San Francisco, presented projections on the effect on HIV transmission of each of these theoretical vaccines and demonstrated that "complete protection for some is better than partial protection for all"—since the latter scenario, in the context of the false security and more risky behavior it is likely to generate, would lead to higher transmission rates. Her work was inspired, she said, by the policy question, "What degree of efficacy is acceptable for an HIV vaccine?"

Asked what he thought of the proffered choice, Nabel presented a "rationale for going forward" in either case. In one scenario, a vaccine that at least blunts the peak of infectivity could be worthwhile, and in the other, figuring out the differences in host factors between populations that react differently to the same vaccine could be worthwhile. As for prospects for a vaccine that would combine the best of both options, he said, "I can't say I know of a vaccine candidate as of now with a good likelihood of succeeding. I think we can do a lot with just CTL [cytotoxic T lymphocyte] immunity, but to achieve a sterilizing vaccine that gives long-lasting protection, we've got to pursue both CTL and neutralizing antibodies—aggressively. My suspicion is that if we cannot generate neutralizing antibodies, we will only see partial protection."

He sees promise in DNA immunization, which he's used in his lab, "not necessarily as a definitive vaccine but as an experimental tool" that allows rapid construction of multiple vectors. The discordant results observed with HIV peptides—good CTL responses with gp160 but not with *nef* and good humoral responses with *nef* but not with gp160—are typical of what he's also seen with Ebola virus, he noted.

He asked whether looking at intrinsic amino acid sequences might not lead to the ability to predict responses to epitopes.

In the translational realm, Nabel noted the need for novel vectors for sustained expression and suggested that lentiviral constructs might be promising. In the clinical realm, comparing the vaccine responses of HIV-infected people on highly active antiretroviral therapy (HAART) with those of uninfected individuals could be "highly informative for both populations," he said.

He expects AIDS vaccine work to be "iterative," that vaccine candidates will continually improve over several generations. And the interest he's observed on campus in the VRC's research agenda—30 to 40 PIs regularly attend VRC planning workshops—has convinced him to formally establish an HIV Vaccine Interest Group. ■

Hot Mouse Tips: a Three-Part Series

Part 1. Improving the Mouse Patient: Perioperative Tips for Better Outcomes

by Tory Hampshire, DVM, NINDS, and Judy Davis, DVM, NINDS

Now that the dawn of mouse phenotyping has arrived, so, too, have more complicated procedures. More often than not, scientists struggle with the issue of anesthesia because of outdated equipment or technique. In this first of a three-part series, we offer you hot methods and tips that may shake up your assumptions and expedite your results inside the mouse facility!

Before You Start

It is important to overcome the tendency to focus on the procedure while being less attendant to the patient's physiological status. Aggressive preparation is critical in small animals—particularly when one is doing simultaneous procedures or back-to-back procedures.

First, the effects of anesthesia on rodent hormones and metabolism have not been fully evaluated. What is known is that any procedure that will produce pain, distress, hypothermia, hypovolemia, dehydration, hypoglycemia, acid-base disturbance, infection, or adrenocortical stress (surgery and anesthesia are big ones) will affect your results in a bigger way than will staving off these adverse effects.

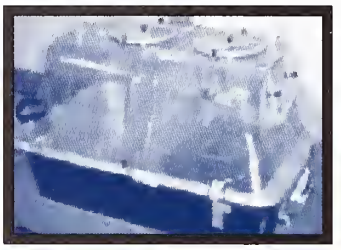
Therefore, consider:

1. Preanesthetic Techniques. Rodents, and mice in particular, have high metabolic rates and small surface areas. Compared with larger animals, they generally require higher anesthetic dosages to achieve an effective level of anesthesia, and the duration is typically shorter. They are also less likely to survive respiratory arrest from overdosage.

Metabolic rate also influences the onset of hypothermia and dehydration from exposed membranes. And even a small amount of surgical blood loss in a mouse may represent a substantial percentage of total blood volume.

Solutions:

- Plan to make provisions for warmth under and over your rodent patient. Heating pads, heat lamps, or even pocket warmers can provide these sources. Accidental burning can be averted by covering the warming pads with polar fleece.
- Assume that your patient will not return to normal drinking patterns immediately and will experience some dehydration. Warmed Lactated Ringers Solution at 60–70 mL/kg/day bolused under the skin before surgery (just after induction of anesthesia) will provide maintenance hydration and help to insulate a mouse during the procedure.
- Drug effects are dose-dependent; an accurate weight is critical! We see this as the most common cause of anesthetic over- and underdosing. Daily weighing postoperatively will also aid in evaluating hydration status and general well-being. Purchase a gram scale and use it daily from the day before surgery to three to five days after. You will be amazed at how much weight rodents lose 12 hours after surgery. Up to 20 percent of body weight can be lost due to decreased fluid intake and increased loss of fluids during surgery.



Two Ways to Warm a Mouse: *(above) an isolated, warmed holding area (Thermocare, Inc., Incline Village, NV, $945–$1060) accommodates several rodents at a time and can receive oxygen through any side port, or (below) a hand-sewn triple-layer of polar fleece can hold a standard single-use pocket warmer in one pocket and a mouse in the other.*

2. Respiration. Most of the time inhalant anesthetic is administered by mask to the mouse because intubation is a challenge given the mouse's small mouth opening, large incisors, large immobile tongue, and large cheek folds. Because rodents are burrowing animals, they have very compliant rib cages. In contrast to larger animals, their functional residual air capacity approximates their vital capacity. When anesthetized, the frequency of respiration decreases while tidal volume remains low. Therefore, minute ventilation is normally maintained with high frequency, low tidal volume, which renders the animal susceptible to respiratory acidosis and hypoxemia. Other considerations include a rodent's propensity to hold its breath and stress-induced catecholamine release.

Solutions:

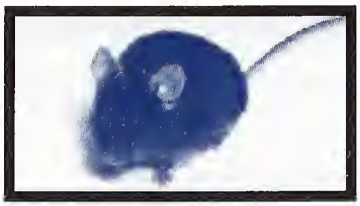
- If you are stuck on injectable anesthesia cocktails, try Dopram (doxapram hydrochloride), a CNS respiratory stimulant, as part of your preanesthetic regimen (one drop, full strength on the tongue).
- Enlist the help of your veterinary section and try to gain access to isoflurane anesthesia and scavenging (downdraft table or hood). Masks made with syringe cases work well. Rodent masks can also be purchased from most veterinary suppliers.
- For procedures likely to last more than 45 minutes, invest in a ventilator and learn to intubate your mouse or rat (see "part 2" in our series).

3. Perioperative Stress and Pain. Diazepam is not effective as a sedative, muscle relaxant, or tranquilizer in most rodents. Alpha-agonists (xylazine, medetomidine) have the potential of undesirable side effects: Sedation often outlasts analgesia, and bradycardia, hypothermia, hyperglycemia, and respiratory depression are not uncommon. Alpha-agonists can be countered, however (consult your veterinarian for reversal agents), and therein lies a strong advantage for their use. Whatever analgesic you choose, you should consider providing it preemptively before noxious stimuli allow pain perception.

Preoperative medications include anticholinergics, anxiolytics, analgesics, respiratory stimulants, and anti-inflammatory drugs. The use of anticholinergics in rodents is controversial. Although they protect against vagal-mediated bradycardia, they increase the viscosity of airway secretions and the potential for obstruction of small airways or the trachea. If you use anticholinergics, you should ventilate the animal vigorously; if you don't use them, you need to monitor heart rate closely.

Solutions:

- To prevent bradycardia, atropine 0.04 mg/kg subcutaneously (SQ) or intramuscularly (IM) 10 minutes before anesthetic induction may be used in concert with Dopram as the respiratory stimulant.
- For narcotic analgesia: buprenorphine hydrochloride 10–20 μg/kg may be



Future articles will discuss new techniques for ventilation, anesthesia, and drug delivery systems for rodents. For more info, call the authors at 301-496-9354, or e-mail to <**hampshiret@ninds.nih.gov**> and <**davisja@ninds.nih.gov**>.

given IM or SQ at onset of immobility and every 6–8 hours thereafter.

■ To reduce pain from local irritants such as stereotactic apparatus, instill lidocaine 2 percent gel in the ear canal and on the ear bars at onset of immobility.

■ For procedures expected to cause severe swelling or visceral pain, Banamine (flunixin) 1 mg/kg SQ may be given twice daily starting at immobility onset [Lactated Ringers fluid and an H_2 blocking agent such as Zantac (ranitidine) 0.5 mg/kg IM or Pepcid (famotidine) 2.5 mg/kg SQ are also recommended to protect against renal and gastrointestinal damage, respectively].

■ To prevent drying of the cornea (keratitis sicca), use a petroleum-based artificial tear ointment. Keratitis sicca is a frequent side effect of anesthesia and is exacerbated by the irritating effect on the eye of anesthesia delivered via face mask. Medications can be obtained from the ORS/VRP pharmacy at **435-2780**.

4. Anesthesia Induction. The most consistent and reliable anesthetic protocols for rodent neonates and adults couple inhalants with vigilant monitoring. Those still using Metofane (methoxy flurane) in a bell jar, think again! Metofane provides little benefit and high risks because of its poor liquid-to-gas coefficient. Rodents are usually either too deep or too light to facilitate safe surgery.

Anesthetic responses to predetermined amounts of injectable anesthetic range from inadequate to death. If you oversee technicians who perform your anesthetic procedures using agents such as barbiturates [Nembutal (pentobarbital sodium) or Pentothal (thiopental sodium)], get them into the habit of using a standard worksheet. We ask our technicians to weigh animals the day before surgery and organize their individual doses for each mouse or rat in small, identified Ziploc bags. Injectable anesthetics have a low margin of safety, often fail to mute peripheral reflexes, and are associated with protracted recovery. If injectables are used, you should monitor heart rate, respiration, and body temperature until the animal is actively moving around the cage. It is common to mistake sternal positioning for "recovery" and to place the animal back in the animal room, which is probably (hopefully) colder than the recovery area; the animal then becomes hypothermic—the metabolic rate falls, and residual anesthesia effectively anesthetizes the animal. Unfortunately, rodents lack the physiological capability to overcome these events, and the outcome can be catastrophic for investigators.

Solutions:

■ If you use the alpha-agonist xylazine, you can use the reversal agent yohimbine (Yobine) 0.25–0.5 mg/kg intravenously to shorten recovery periods. If you are not expert at tail vein injections, you can give this drug IM using a 25-gauge or smaller needle.

This small Plexiglas box and inhalant anesthesia system work for rapid induction and recovery under isoflurane gas anesthesia. Here it is used under a hood, but the system also works nicely over a down-draft surface, provided the operator guards against a chilled mouse bottom.

■ Use of a small Plexiglas box is preferred for inhalant anesthesia induction. Once the animal is anesthetized, it is removed from the chamber and switched to a face mask or a multiple-mouse port manifold for maintenance (if you need up to six animals anesthetized at once). This achieves the benefit of using oxygen flow over liquid anesthetic to produce the plane of anesthesia desired. Recovery from inhalation anesthesia is also very rapid. As a tip, consider oxygenation (100 percent) for 5 minutes prior to induction and on recovery to ensure that hypercapnia does not develop. Isoflurane with a calibrated vaporizer is the method of choice in terms of patient safety and lack of environmental contamination (details on vaporizers and components next article).

5. Anesthesia Maintenance. Solutions:

■ Facilitate good depth of anesthesia with injectable combinations like ketamine-xylazine cocktails by using a topical local anesthetic whenever possible along the incision line—0.1–0.2 mL of 2 percent mepivacaine or lidocaine under the skin at the surgical site will enhance analgesia and better facilitate immobility. It will also lower the needed anesthetic dose.

■ Whenever possible, use nonrebreathing systems with oxygen flow at least three times the minute ventilation (10 mL/kg or about 0.2 mL/mouse) to lower CO_2.

■ Take precautions against patient cooling, which is increased with high oxygen flow rates. Because the mean alveolar concentration of anesthetic (MAC) needed falls with falling body temperature, you must lower your anesthetic concentration to prevent anesthetic overdosage if your mouse chills. Monitor body temperature, and adjust MAC accordingly.

■ Surgical procedures invite pH disturbance. Remember: Rodents normally maintain minute ventilation by high respiratory rates and low tidal volumes. During anesthesia, both tidal volume and minute ventilation fall; therefore, if you don't ventilate, you risk respiratory acidosis with or without hypoxemia.

If you anticipate long procedures (greater than 45 minutes), learn to ventilate your rat or mouse. Special machines can be purchased from several suppliers to achieve high-frequency ventilation in small tidal volumes for rodents (details next article).

6. Recovery Support. High metabolic rate, a high ratio of surface area to weight, and high oxygen flow rate lead to a faster rate of cooling in rodents than in larger animals. It is *critical* that they are kept warm until they are fully ambulatory. If you have a means of monitoring temperature, all the better! pH disturbances are also common and can be kept minimal by shortening anesthesia time; reliable pH monitoring is now possible in rats but not yet in mice.

Solutions:

■ Consider purchasing a pulse oximeter to measure saturated oxygen concentration. This equipment has reasonable efficacy in the rat when body temperature is conserved to the tail. In mice, however, blood flow in the tail, foot, and tongue is not great enough to yield reliable readings.

Dedicated rodent thermometers can be purchased (Physiotemp, Clifton, NJ) with rectal probes for more accurate temperature assessment.

■ Environmental space room temperature should be kept with the mouse in mind, not the surgeon. Warm water-circulating blankets, warm lavage intraoperatively, plastic wrap for insulation, pocket warmers, or used pediatric isolation units make good provisions for warmth. Keep a small rodent recovery room or area that can be separated from the standard mouse or rat room. The isolette shown in this article (p. 8) is also useful for this purpose if you do not have a separate room. Some companies are now engineering mouse racks with thermal elements so that individual rows can be warmed.

■ Remember that your mouse or rat patient may not feel well enough to eat or drink for the next few days. Add fresh fruit, Jell-O cubes, or extra doses of subcutaneous fluid boluses to your postoperative regime.

■ Work with your institute veterinary staff to develop pain scoring for your mouse or rat based on subjective and objective indicators. This will help in making analgesic redosing decisions.

■ You should worry about infections if your procedure is long and complications occur. You can run a complete blood count (Clinical Center lab **496-3386**) by obtaining an orbital blood sample in a heparinized hematocrit tube. Your institute vet can also prescribe a prophylactic antibiotic for your patient.

Institution of as many of these tips for periprocedural care of the mouse and rat will result in less wasted time, greater survival rates, and, best of all, comfortable animals. Common use of these materials and procedures can't be anything other than a win-win situation in the world of animal research and research support. ■

Disclaimer: *Mention of specific products in this article does not constitute an endorsement of those products, nor does it signify that other similar products are less desirable.*

High-Calorie Mouse Jell-O
-2 cups boiling water
-1 pkg. raspberry-flavor Jell-O
-60 mLStat-VME (VRP Pharmacy)
-20 mLPediasure (VRP Pharmacy)
-2 scoops Designer Protein (GNC Health Food Store)
Blend well and refrigerate in ice-cube trays. Serve one-quarter cube per mouse per day.

Help Wanted: FAES School Director

If shaping a curriculum interests you as much as designing an experiment, the Foundation for Advanced Education in the Sciences (FAES) may have a job for you. FAES is seeking a scientist to serve as director for its courses taught at NIH, a 40-year-old education program that has an enrollment of more than 2,500 students and offers nearly 200 courses. The part-time position is being vacated by NIDDK's Paul Torrence, who is moving to Northern Arizona University as professor and chairman of chemistry. The new director must be a scientist familiar with NIH and its science education needs (but need not be employed by NIH) who can develop a new curriculum that uses a modern molecular biology teaching lab. For more info, contact Lois Kochanski at FAES (301-496-7975; e-mail: **<kochanskil@faes.od.nih.gov>**.

Attn: Catalyst Mailees

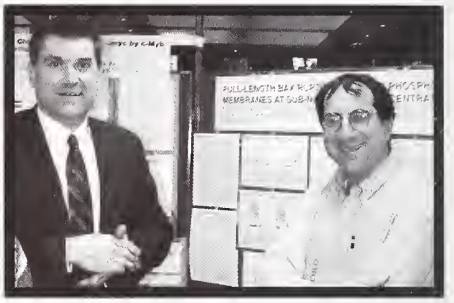
Whoever receives *The NIH Catalyst* in their very own mailbox is herein advised to look at the mailing address on the back page and see if it includes an MSC number. If not, please send your MSC number, along with your name and mailing address, to **<wallacea@ors.od.nih.gov>** or fax it to 402-0217. This is the only way to ensure continued deliverance (of the *Catalyst* to your mailbox). ■

Tech Transfer Seminar

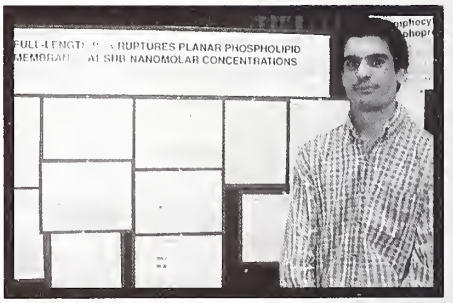
A technology transfer seminar for scientists—how to interact with the biotech and pharmaceutical community—will be held Thursday June 3, from 9:00 a.m. to 4:00 p.m. in Wilson Hall, Building 1. To be covered are the collaborative process, inventions and patentability, and how scientists can share in the royalty income stream that derives from their scientific efforts. For more information or reasonable accommodations, contact Lauren Neal at **<lauren.neal@nih.gov>**. ■

All's FARE . . .

There were 130 winners in the fifth annual FARE (Fellows Award for Research Excellence, 1999) competition, and the NIH community has been having the opportunity to view these FAREST of them all each Wednesday when, in conjunction with the Wednesday Afternoon Lectures, sets of related winning posters are on display outside the Visitor's Information Center in Building 10, a few feet away from the doors to Masur Auditorium, where the lecture takes place.



WALS lecturer Craig Thompson (left) and NICHD's Josh Zimmerberg, mentor to FARE winner in photo below



Gorka Basanez demonstrates how "Full-Length Bax Ruptures Planar Phospholipid Membranes at Subnanomolar Concentrations."

The lectures and posters will continue through June 30. Following are descriptions of the FARE wares of Wednesday, April 14.

Five of the winners presented posters of their work related to the talk (sponsored by the Apoptosis and Cell Biology Interest Group) given by Craig Thompson of the University of Chicago on "Keeping Cells Alive: Is Caspase Inhibition Enough?"

Certain extracellular signals activate intracellular proteins that regulate the process of cell death. In his talk, Thompson highlighted the role of mitochondria in apoptosis, or programmed cell

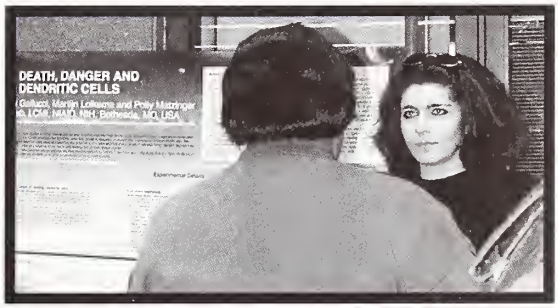
. . . In (Cell) Life and Death

text and photos by Ramie Leibnitz, PhD, NCI

death. One of the Bcl-2 family of proteins, Bcl-x_L, appears to form a pore in the outer membrane of the mitochondria.

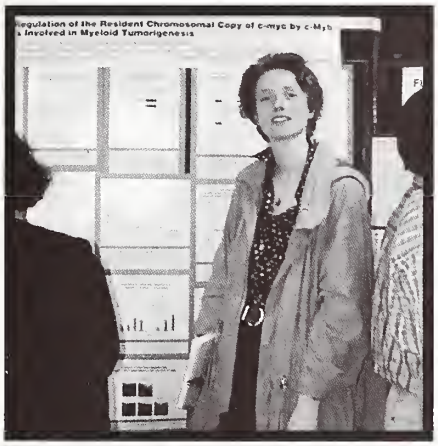
This leads to loss of membrane potential and influences activation of the caspase enzymes, which ultimately mediate apoptosis.

How signals through cell surface receptors influence the bioenergetics of a cell remains a complex issue in the study of apoptosis.



Stefania Gallucci unfolds the drama of "Death, Danger, and Dendritic Cells."

The posters described research of



Martina Schmidt elucidates how the "Regulation of the Resident Chromosomal Copy of c-myc by c-Myb Is Involved in Myeloid Tumorigenesis."

both positive and negative signals leading to cellular apoptosis or activation. The work by **Gorka Basanez,** conducted in the NICHD Laboratory of Cellular and Molecular Biophysics with Josh Zimmerberg, corroborated Thompson's talk by demonstrating the effect of the protein Bax on mitochondrial membrane stability.

"We studied pore formation by Bax and found that the pore is partially composed of lipid—it's not purely protein," Basanez said, noting that full-length Bax caused conductance changes that led to rupture of planar phospholipid membranes at very low protein concentrations.

This work implies that Bax may act directly on mitochondrial membranes, said Basanez, who intends to continue in basic research in either the United States or his native Spain.

Defects in the apoptotic signal cascade can have clinical manifestations, and **Jin Wang**, who generally can be found in Mike Lenardo's lab in the NIAID Laboratory of Immunology, showed that a mutation within caspase 10 disrupts lymphocyte apoptosis and provides an explanation for some cases of autoimmune lymphoproliferative syndrome.

His exposure as a FARE recipient, Wang said, has expanded his contacts and opportunities to discuss his research with NIH colleagues. In an otherwise normal day, he said, "Not many people come to the 11th floor" (of the Clinical Center).

Martina Schmidt, whose research was conducted with Linda Wolff in the NCI Laboratory of Cellular Oncology, demonstrated for the first time that inappropriate regulation of a transcriptional activator called Myb can disregulate the chromosomal copy of the *Myc* gene and enhance cellular proliferation.

Schmidt said she wants to continue studying other genes activated by Myb that are involved in myeloid tumor formation.

A similar stimulatory relationship akin to that in Schmidt's laboratory exists between activated cells and HIV in **Jeff Schrager**'s research world. From his base in the NIMH Laboratory of Molecular Biology, with Jon Marsh, Schrager showed that the HIV protein called Nef lowers the threshold for activation in T cells and allows enhanced replication of the virus.

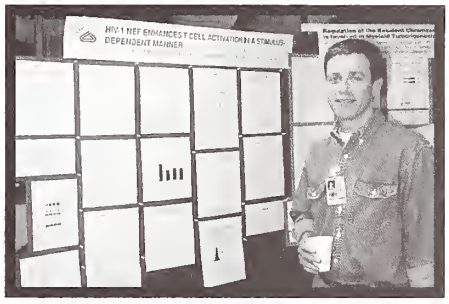
Jin Wang elaborates on the "Inherited Caspase-10 Mutation in the Human Autoimmune-Lymphoproliferative System."

Without Nef, HIV replication is diminished, and infection would not progress to AIDS.

Schrager used his FARE travel award to present his work at the AIDS Pathogenesis Keystone meeting in January. Come the fall, he'll be moving from NIMH to NCI for pathology training.

Stefania Gallucci's work in NIAID provides initial evidence to support the "Danger Model," which predicts that damaged or necrotic tissue sends an alarm to activate the immune response.

Programmed cell death provides a



Jeffrey Schrager explains how "HIV-1 Nef Enhances T-Cell Activation in a Stimulus-Dependent Manner."

means to delete cells without activating the immune response, and Gallucci found that dendritic cells become activated only after incubation with necrotic fibroblasts, not with apoptotic cells.

Gallucci works in Polly Matzinger's lab in NIAID's Laboratory of Cellular and Molecular Immunology—also known as the "Ghost Lab," she said. Her award for the research done there, however, is far more visible and has given her "recognition that I'm doing a good job—not only from my boss but from other postdocs."

These five, like all 130 FARE winners are presenting their research at meetings—with travel travel support from their $1000 FARE travel awards.

Twenty percent of applicants were winners in the 1999 competition; next year the percentage will be upped to 25 percent. ■

People

Recently Tenured

Amy Hauck Newman *received her Ph.D. in medicinal chemistry from the Medical College of Virginia in Richmond in 1985 and postdoctoral training in the Laboratory of Medicinal Chemistry, NIDDK. She was a research chemist at Walter Reed Army Institute of Research from 1988 to 1990, when she became a senior staff fellow at NIDA, where she initiated a medicinal chemistry research program in the Psychobiology Section. She is now a senior investigator and chief of the Medicinal Chemistry Section at NIDA.*

My research interests are in the design and synthesis of highly selective ligands for the characterization of the protein targets of psychomotor stimulants and the development of medications to treat stimulant abuse.

Fran Pollner

Amy Hauck Newman

It is well known that cocaine binds to dopamine, serotonin, and norepinephrine transporters and thereby inhibits reuptake of their respective neurotransmitters.

The mechanism(s) underlying the reinforcing, or addictive, effects of cocaine, however, appears to primarily involve the inhibition of dopamine uptake. Thus, we directed our efforts toward designing novel ligands with high affinity and selectivity for the dopamine transporter.

Our initial synthetic studies were based on structural modification of a known dopamine-uptake inhibitor and treatment for Parkinson's disease, benztropine. This molecule shares several structural features with both cocaine and another known dopamine-uptake inhibitor, GBR 12909, but does not show reinforcing effects in animal models of drug abuse.

By developing novel compounds with benztropine as the parent ligand, we could make structural and pharmacological comparisons with cocaine and learn more about drug-transporter interactions and how these translate into the behavioral effects of these drugs.

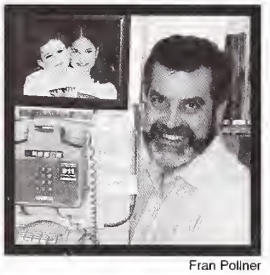
Through these studies, we discovered a novel series of ligands that binds with high affinity to the dopamine transporter and inhibits dopamine uptake. However, in comparison with cocaine, this series of compounds is selective for the dopamine transporter and is distinct in chemical structure, structure-activity relationships, and behavioral profile. Specifically, animals treated with these dopamine-uptake inhibitors do not demonstrate cocaine-like behavior typical of psychostimulant abuse, and some of the compounds attenuate cocaine-induced behaviors. Based on these findings, we hypothesized that these benztropine-based ligands interact at a binding domain on the dopamine transporter that is different from that of cocaine and may thus lead to behaviors unlike those associated with cocaine use.

We recently synthesized a novel photoaffinity label that we used in immunologic and proteolytic mapping to demonstrate that, in fact, this ligand labels a binding domain in the 1-2 transmembrane region of the dopamine transporter, rather than the 4-7 transmembrane region labeled by a cocaine-based photoaffinity ligand. We are currently designing cysteine residue–specific irreversible ligands that will allow the structural elucidation of the binding domain of these dopamine uptake inhibitors and will relate them to function of this protein.

We are also studying other structurally diverse classes of compounds to further characterize the dopamine transporter and other systems that may be related to cocaine abuse, such as the dopamine D_3 receptor subtype. We are developing both two- and three-dimensional quantitative structure-activity relationship models as an approach that complements classical rational drug design and that will allow us to identify new lead compounds for future chemical modification.

We hope that by elucidating mechanisms underlying the reinforcing effects of cocaine, through the use of precise molecular probes, we may ultimately be able to design therapeutics for the treatment of cocaine abuse.

Marc Reitman *received his M.D. and Ph.D. degrees from Washington University in St. Louis in 1983. He then did a residency in internal medicine at New York's Columbia-Presbyterian Hospital before coming to NIH in 1986 as a clinical fellow in the NIDDK Laboratory of Molecular Biology. He is now a senior investigator in the Diabetes Branch, NIDDK.*



Fran Pollner

Marc Reitman

I am interested in the molecular mechanisms regulating body weight and metabolic efficiency. Obesity is a major medical problem that particularly increases the risk of diabetes, lipid abnormalities, and hypertension. Genetic background contributes greatly to an individual's chances of being obese.

In spite of the magnitude of this problem, surprisingly little is understood about the genes and molecular mechanisms underlying obesity and how obesity predisposes to diabetes. My laboratory focuses on developing and characterizing mouse models to understand the genetic contributions to obesity and diabetes.

The discovery of leptin in 1994 inspired my study of energy homeostasis. Since obesity and diabetes are properties of the whole animal, it became clear that we would also need to study whole animal physiology.

We concentrate on the mouse to take advantage of knockout and transgenic mutants, and we have developed the ability to measure metabolic rate and to continuously monitor body temperature.

Three projects are ongoing in the laboratory: regulation of leptin expression, characterization of uncoupling protein-3, and analysis of a transgenic mouse that is nearly devoid of white adipose tissue.

Leptin is a hormone secreted from adipose cells in proportion to fat mass, signaling stored energy levels to the rest of the body, particularly the hypothalamus. Leptin controls energy intake, metabolic efficiency, and energy expenditure. A low leptin level signals the body to conserve energy.

We are interested in how leptin expression is regulated. One step toward understanding this was our identification of promoter elements that mediate adipose-selective expression. Another key issue under investigation is how adipocyte fat content regulates leptin transcription.

We have also studied the biology of leptin in pregnancy, when circulating leptin levels increase. In humans, the

2-fold increase is due to placental transcription driven by a placenta-selective enhancer. In contrast, in mice, leptin rises 20-fold during gestation, but is not made in the placenta. Instead, the placenta makes a binding protein (soluble leptin receptor) that prevents leptin clearance. The roles of leptin during pregnancy are not clear, and they may even be different between species.

A fundamental observation central to research in this field is that the body "defends" or strives to maintain its weight by becoming more metabolically efficient after weight loss and less efficient upon weight gain. This is one of the reasons that dieting to lose weight is so difficult and frustrating. The molecular bases for these adaptations are unknown, but presumably include changing the flux through inefficient and/or futile metabolic cycles.

In 1997, we (and others independently) discovered uncoupling protein-3 (UCP3). This nuclear gene encodes a protein that is predicted to cause a mitochondrial proton leak. We have shown that UCP3 will reduce the mitochondrial membrane potential when expressed in yeast. UCP3 is expressed in muscle and is upregulated by thyroid hormone. Taken together, these data suggest that UCP3 has a role in the regulation of metabolic rate and efficiency. We have made and are currently characterizing a UCP3 knockout mouse to test these hypotheses.

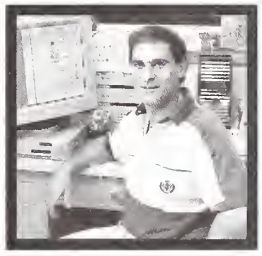
In collaboration with Charles Vinson's laboratory (NCI), we generated a transgenic mouse, named A-ZIP/F-1, that is virtually devoid of white fat. This was achieved using an adipocyte-specific promoter to drive expression of a dominant negative protein. The dominant negative protein inactivates certain basic-zipper transcription factors, preventing cell proliferation and differentiation. The A-ZIP/F-1 mice are diabetic, with a phenotype remarkably similar to that of humans with severe lipoatrophic diabetes.

Using transplantation to reverse the phenotype, we showed that it is the adipose tissue deficit that causes the diabetes. This is in stark contrast to the usual type 2 diabetes, which is associated with obesity. Thus the A-ZIP/F-1 mice are a model of a paradoxical, poorly understood form of diabetes and also allow the study of the physiologic roles of fat.

Thomas Schneider *received his Ph.D. from the University of Colorado, Boulder, in 1984. He continued the same project, on molecular information theory, in both his postdoctoral work and at NIH in the Laboratory of Experimental and Computational Biology, NCI, where he is a senior investigator.*

If you want to understand life, don't think about vibrant, throbbing gels and oozes, think about information technology.
—Richard Dawkins, *The Blind Watchmaker*, 1986

I believe that living things are so beautiful that there must be a mathematics that describes them. In 1978, in the lab of Larry Gold in Boulder, Colorado, I started looking for mathematical ways to describe ribosome binding sites. I was working with frequency tables of the bases in the sites and gave a talk to some computer scientists. After the presentation, Andrzej Ehrenfeucht, the head of the group, suggested, "Why don't you try the information transform?" I asked, "What's that?" He wrote "p log p" on the blackboard. I asked, "What does that mean?" "Oh, you go look it up!"



Thomas Schneider

Half a year later I got around to computing the information, and got 11.0 bits. But what did that mean? I soon realized that I could also compute how much information would be needed to find the binding sites, given the size of the genome and number of binding sites. I was stunned to get 10.6 bits. I was able to confirm for other genetic systems that the sequence conservation at binding sites (Rsequence, measured in bits) is close to the information needed to find them (Rfrequency, also in bits). That discovery launched my career.

At first, describing ribosomal processes in terms of information may seem simple. After all, it's trivial to compute the expected frequency of *Eco*R I sites (5' GAATTC 3') as one in 4096 random bases. However, for ribosomes, the size of the genome and number of genes are fixed by physiology and history, but the patterns at the sites could be anything.

Indeed, I soon discovered that the region around bacteriophage T7 promoters has 35.4 bits, but only 16.5 bits are needed to find them. Either the budding theory—that binding site conservation evolves to match the minimum information needed to find the sites in the genome—was wrong or the data were telling us something new. I set out to do experimental work on these promoters. After four years of attempting to select for functional promoters, I found out that a functional T7 promoter will kill cells within three minutes of induction. To get around this problem, I used a toothpicking screen to isolate functional promoters from a chemically synthesized random library of T7 promoter variants. The variations destroyed the excess information, and I found that the polymerase only needs 18.2 bits to be strong enough to kill cells. Presumably the excess information represents the binding sites of another protein; we are hunting for it in the lab.

I found information theory extremely fruitful for describing binding sites in more than 50 genetic systems. At my web site, <**http://www.lecb.ncifcrf.gov/~toms/**>, you will see two kinds of pretty graphics: sequence logos and sequence walkers. I invented sequence logos with my first Werner H. Kirsten Student Intern Program high school student, Mike Stephens. Using information to measure the sequence conservation at each position across a binding site, they represent an average picture of a collection of binding sites. They replace consensus sequences for making a picture of what sites look like and can show which face of the DNA a protein binds to. The area under a logo is Rsequence.

Logos give only an average picture. Can we assign an information content value to each individual binding site sequence so that their average is Rsequence? Marvelously, the mathematics "melts in your mind" to give a simple formula. My friend John Spouge (NCBI, NLM) then proved that this is the only possible formula that satisfies the averaging criterion.

My friend Pete Rogan (ABL, now at Children's Mercy Hospital, Kansas City, Missouri) found a paper claiming that a certain T-to-C change at a splice junction in hMSH2 caused colon cancer. Pete looked at our splice acceptor logo and realized that nearly 50 percent of the time there are Cs there. The people working on hMSH2 had forgotten the

original data when they made their consensus sequence! Bert Vogelstein showed that 2 of 20 normal people have the change, so it is indeed a polymorphism. This case convinced us that information theory would be useful in predicting splicing effects in key disease genes.

To show how splice-junction changes affect the individual information content, I invented a computer graphic that "walks" across a sequence at one's command. With these sequence walkers, complicated splice-junction mutations can be understood in seconds. One of my favorite cases is a low information content cryptic site lurking next to a strong normal site that is sitting on the end of an exon. A mutation of the sequence drops the information content of the site while simultaneously (!) raising the information content of the cryptic, which takes over. Since the cryptic site is out of frame, the protein is destroyed. We have analyzed more than 100 human splice-junction mutations using information theory. Jim Ellis (OD/ORS/BEPSP) has recently joined us. He is handling several international collaborations and is also set up on the main campus to do these analyses for scientists at NIH [see box this page].

In 1983, I set out to understand how the information values I was measuring are related to the binding energy. The data were indicating a proportionality. What did that mean? Claude Shannon, who developed information theory 50 years ago, not only gave us a way to measure the amount of information, but also a way to determine how much information can be sent through a communications channel. This "channel capacity" is determined by the thermal noise and the energy dissipated. It can be used to find the maximum information that can be gained for a given energy dissipation. Surprisingly, I found that this is a new version of the Second Law of Thermodynamics. Using this, I was able to convert my proportionality to an efficiency of 70 percent. This means that 30 percent of the binding energy is "wasted" because it is dissipated but does not contribute to the choices being made. Why?

The mystery deepened when I stumbled on the fact that the quantum efficiency of rhodopsin is also 70 percent. That is, for every 100 photons that are absorbed and that excite a rhodopsin molecule, only in 70 cases does the rhodopsin change states. Later, at a lecture on muscle, I guessed that muscular efficiency would be the same, and was surprised to find that it is.

I went deeper into the theory and in 1989 found an elegant, purely geometric answer that explains why so many molecular machines are 70 percent efficient. I've been trying to finish the publications ever since then!

Where will this lead us? Information theory has proven itself in hundreds of genetic systems, and the door is now open for understanding any molecular interaction or state change using these well developed mathematical tools. In particular, I think the key to the future is coding theory. Fortunately, communications engineers have not been idle for the last 50 years. Telephone clarity, crisp CD music, and reliable Internet protocols are all based on the error-correcting codes predicted by Shannon. We are now in the same position in biology: There must be codes for molecular interactions; we only need to find them. Sequence logos and walkers appear to be a good start.

Knowledge of information theory in biological systems can enlighten molecular design and provide a theoretical grounding for nanotechnology. In my lab, the theory has led to our inventing a practical molecular computer, which is patent pending. Three other patentable nanotechnology projects are also in the works. ■

JSPS Fellowships for the Year 2000

June 11 is the deadline to apply for a Japan Society for the Promotion of Science (JSPS) fellowship beginning in the year 2000 on either January 1, February 1, or March 1.

The fellowship is sponsored by the JSPS, in cooperation with NIH's Fogarty International Center (FIC) and the NIH Office of Intramural Research. Twenty fellowships are awarded annually; they last up to two years and carry a monthly stipend of 354,000 yen provided by JSPS.

Candidates must have a funding commitment from NIH and a tangible (not photocopied) doctoral degree. They must be under 34 years old as of April 1, 1999 (or under 36 if their degree is in medicine, dental science, or veterinary medicine). They must be Japanese citizens or permanent residents of Japan who intend to have research positions at universities or other academic institutions in Japan.

Fellowship winners are required to prepare and submit an annual report on their research progress—in Japanese to JSPS and in English to the scientific director and supervisor of their host laboratory at NIH and to FIC.

June 11: Deadline for receipt of applications to FIC (in both Japanese and English). July 28: NIH review committee nominates top 30 applicants to JSPS. September 16: JSPS mails out preliminary letters of selection to fellowship awardees and notifies NIH. January1, February 1, March 1, 2000: Stipends awarded.

For application forms, and further information please contact: Kathleen Michels, JSPS Programs, Division of International Training and Research, FIC, NIH, Bldg. 31, Room B2C39, Bethesda, MD 20892-2220; 301 496-1653; fax: 301 402-0779; e-mail: <**jsps@nih.gov**>. ■

Splice Junction Site

Jim Ellis (OD/ORS/BEPSP) has set up Tom Schneider's Delila programs to do splice junction analyses for scientists at NIH.

Published or unpublished sequence data can be used, but it is most efficient to start with GenBank flat file format.

Other change or mutation specifications are acceptable, but the process may be a bit less efficient. The user does not have to learn Delila to use the service or obtain results.

A GenBank accession number (or the sequence) and the sequence changes are needed to begin the analysis. Specification on a floppy disk or by e-mail is preferred. See <**http://www.lecb.ncifcrf.gov/~toms/spliceanalysis.html**> for further information.

Ellis can be found at Building 13, Room 3W-16A; phone: 301-496-4472, fax: 301-496-6608; e-mail: <**ellisj@ors.od.nih.gov**>.

In a Blaese of Glory

Michael Blaese: Profiled

Michael Blaese came to NIH in 1966 as a clinical associate at NCI, where he worked in the lab of Tom Waldmann, now chief of NCI's Metabolism Branch.

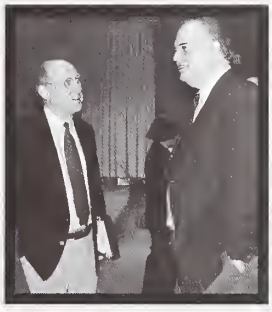
By the time he moved over to NHGRI in 1994 to lead the clinical gene therapy program, Blaese had pioneered the first gene therapy treatment trial in the country. He and his colleagues French Anderson (then at NHLBI and now at the USC School of Medicine in Los Angeles, where he directs the Gene Therapy Laboratories) and Ken Culver (then at NICHD and now pharmacogenetics head at Novartis in East Hanover, New Jersey) used a retroviral vector to deliver corrective genes to patients born with adenosine deaminase immune deficiency. The historic moment that Blaese's gene therapy protocol was approved by the NIH Recombinant DNA Advisory Committee (RAC) in 1990 was shared by NCI surgery chief Steve Rosenberg, whose own protocol to deliver IL-2 genes into tumor infiltrating lymphocytes in the treatment of melanoma also won approval at that RAC session.

Last year, Blaese made known his plans to leave NIH and on April 15 a gene therapy seminar was held here to honor him and wish him well in his new position as chief scientific officer and president of the molecular pharmaceuticals division of Kimeragen, Inc., of Newtown, Pennsylvania. ■

The Past Is Prologue

Recalling his early assignment as NHGRI director to establish an intramural research program in genomics and genetics, Francis Collins (right) recounted how he "wandered the corridors of Building 10, got lost, stumbled into an office the size of a closet, and there found Mike—a scientist with an international reputation with the obvious modesty not to ask for more space." In Mike Blaese, he said, was the "marriage of a sharp mind and a gentle spirit." Former gene therapy collaborator French Anderson (left) described continuing research that may lead to protocols for in utero gene therapy in the future. The approach, he said, is in vivo retroviral-mediated gene transfer into autologous blood cells at 17–20 weeks. Timing early in the second trimester moves beyond the first-trimester risk of germline involvement and also seizes the time when stem cells are most actively dividing and amenable to gene transfer, he noted.

Said Steve Rosenberg (left) of colleague Mike Blaese (right): "Mike has no concern about credit . . . . there is a solidness to him."



Generations: *As Tom Waldmann (left), his first NIH mentor, put it, Mike Blaese (right) has provided "definitive answers for questions that couldn't even be asked three decades ago." Giovanna Tosato (bottom), a former student of Blaese, now director of hematologic products at the FDA's Center for Biologics Evaluation and Research, credited Blaese with sharpening her research focus.*

—text and photos by Fran Pollner

Just Awards

Joan P. Schwartz

Torch Passers: *Hynda Kleinman (right), chief of the Cell Biology Section at NIDCR, on the occasion of her receipt of the annual award for Excellence in Mentoring, conferred by the Bethesda chapter of American Women in Science (AWIS). Sharing the moment with her is Ruth Kirschstein, NIH deputy director and recipient of the award in 1997.*

Fran Pollner

Another NIH Feather in NAS Cap: *Robert Desimone (left), NIMH scientific director and chief of the Laboratory of Neuropsychology, looking modest at celebration to honor his election into the National Academy of Sciences, as boss Steve Hyman, NIMH director, joins in the congratulations. Also elected to the Academy was John Coffin, head of the NCI FCRDC viral resistance program.*

Call for Catalytic Reactions

In this issue, we are asking for your reactions in four areas: public input to NIH research directions, vaccine priorities, an NIH graduate program, and E-biomed.

Send your responses on these topics or your comments on other intramural research concerns to us via e-mail: <catalyst@nih.gov>; fax:402-4303; or mail: Building 1, Room 209.

In Future Issues...

- July Update: Interest Groups
- On the Edge Of E-biomed
- Proteomics

1) The Committee of Public Representatives (COPR) has had its first meeting (see page 1). What is your general reaction to the existence of such a group? How can it prove most valuable to NIH research efforts?

2) What are your thoughts on the Vaccine Research Center?

3) A town meeting on the proposed NIH graduate program was held May 24. Tell us what you thought of what was said and your own ideas about the issue.

4) On the bottom of page 5 of this issue is a little box announcing a URL address for the E-biomed proposal. Check it out and in addition to e-mailing your response online, if you are so inclined, send us your reactions as well. We're planning on covering the whole idea in a near-future issue.

The NIH Catalyst is published bi-monthly for and by the intramural scientists at NIH. Address correspondence to Building 1, Room 209, NIH, Bethesda, MD 20892. Ph: (301) 402-1449; fax: (301) 402-4303; e-mail: <catalyst@nih.gov>

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